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# ALTERATION OF RADIATION EFFECTS BY 2-(n-DECYLAMINO) ETHANETHIOSULFURIC ACID (WR1607) IN THE MONKEY

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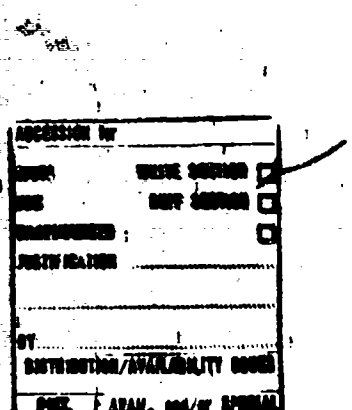

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2-(n-decylamino) ethanethiosulfuric acid (WR1607) was given to trained and untrained monkeys (10 mg/kg) 30 minutes prior to irradiation to investigate its effects on behavior and physiology during the early transient incapacitation period. Catheters to monitor aortic and venous pressures, heart rate and respiratory rate were surgically implanted in the untrained monkeys. The trained monkeys were trained to perform a shock motivated visual discrimination task. Following the injection of WR1607 a significant increase occurred in aortic pressure with a significant decrease in heart rate. No significant changes in percent correct trials or latency occurred following injection. The untrained injected animals were irradiated with a pulse of 2500, 4000 or 15,000 rads of mixed gamma-neutron radiation. After irradiation a significant decrease in aortic pressure occurred from 2-4 minutes in the 2500-rad group and from 1-2 minutes in the 15,000-rad group. After irradiation the respiratory rate increased significantly in all injected groups. Trained injected monkeys irradiated with a pulse of 2500 or 4000 rads did not display a decrease in performance during the early incapacitation period (0-20 minutes postirradiation). Trained monkeys not receiving the drug displayed a decrease in performance below a 90 percent correct response level in both the 2500- and 4000-rad groups. The physiology and behavior of treated and untreated animals were not significantly different after the first 20-minute postirradiation period.

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## FOREWORD
(Nontechnical summary)

Numerous chemicals have been investigated to determine their ability to attenuate the effects of radiation injury. Most of the chemicals have been tested at radiation doses in the $LD_{50/30}$ range using increased survival as indicators of protection. Sulfur containing N-substituted aliphatic amines have been found to be among the most promising radioprotective agents. One of these compounds 2-(n-decylamino) ethanethiosulfuric acid (WR1607) has been found to also alleviate the early transient incapacitation (ETI) observed in the monkey following a dose of 10,000, 20,000 or 40,000 rads. This indicates that WR1607 is capable of attenuating radiation effects over a very broad dose range.

In the present study WR1607 was given to monkeys prior to irradiation to investigate the effects of the compound on behavior and physiology during the ETI period. WR1607 was injected intravenously (10 mg/kg) 30 minutes before irradiation. Following the injection of WR1607 the animals appeared to become very apprehensive with increased movement and vocalization in the restraining chair. This period of increased activity lasted for 7-10 minutes postinjection and usually ended with the animal vomiting. After injection of WR1607 the aortic pressure increased and the heart rate decreased. However, the animals' ability to perform a learned task was not impaired during the period following injection.

The animals that were surgically implanted to monitor aortic and venous pressure, heart rate and respiratory rate were injected with WR1607 and irradiated with a pulse of 2500, 4000 or 15,000 rads of mixed gamma-neutron radiation. After

irradiation, the respiratory rate increased in all radiation groups. The aortic pressure decreased below the elevated postinjection values and was significantly lower than the preinjection values from 2-4 minutes postirradiation in the 2500-rad group and from 1-2 minutes postirradiation in the 15,000-rad group. The aortic pressure values in the 4000-rad group were not significantly different from preinjection values.

The animals trained to perform a learned task were irradiated with a pulsed dose of 2500 or 4000 rads of mixed gamma-neutron radiation. Half of the trained animals in each group were injected with WR1607. Following irradiation the injected groups of animals maintained performance values near preirradiation levels until 60-80 minutes postirradiation. The noninjected groups displayed a performance decrement during the first 20 minutes postirradiation. After the first 20-minute behavioral session the performance of the noninjected animals and WR1607 injected animals was not significantly different.

The compound WR1607 is a radioprotective agent which appears capable of alleviating the ETI period observed in the monkey following a supralethal dose of radiation. The mechanism by which WR1607 prevents ETI or the mechanism by which it attenuates radiation injury in the lethal dose range is at present speculative. The mechanisms which may be involved and physiological and behavioral changes found in the present study are discussed.

## ABSTRACT

2-(n-decylamino) ethanethiosulfuric acid (WR1607) was given to trained and untrained monkeys (10 mg/kg) 30 minutes prior to irradiation to investigate its effects on behavior and physiology during the early transient incapacitation period. Catheters to monitor aortic and venous pressures, heart rate and respiratory rate were surgically implanted in the untrained monkeys. The trained monkeys were trained to perform a shock motivated visual discrimination task. Following the injection of WR1607 a significant increase occurred in aortic pressure with a significant decrease in heart rate. No significant changes in percent correct trials or latency occurred following injection. The untrained injected animals were irradiated with a pulse of 2500, 4000 or 15,000 rads of mixed gamma-neutron radiation. After irradiation a significant decrease in aortic pressure occurred from 2-4 minutes in the 2500-rad group and from 1-2 minutes in the 15,000-rad group. After irradiation the respiratory rate increased significantly in all injected groups. Trained injected monkeys irradiated with a pulse of 2500 or 4000 rads did not display a decrease in performance during the early incapacitation period (0-20 minutes postirradiation). Trained monkeys not receiving the drug displayed a decrease in performance below a 90 percent correct response level in both the 2500- and 4000-rad groups. The physiology and behavior of treated and untreated animals were not significantly different after the first 20-minute postirradiation period.

## I. INTRODUCTION

Many compounds have been investigated to determine their ability to attenuate radiation effects in animals receiving a control $LD_{50/30}$ to $LD_{99/30}$ radiation dose.[9, 15] Several sulfur containing N-substituted aliphatic amines have been shown to have radioprotective properties.[3, 5] One of these compounds 2-(n-decylamino) ethanethiosulfuric acid (WR1607) was found to also alleviate the early transient incapacitation (ETI) observed in the monkey following a dose of 10,000, 20,000 or 40,000 rads.[10] This compound (WR1607) prevented adrenergic vasodilation by phenoxybenzamine in the dog and restored the pressor effect of epinephrine following alpha adrenergic blockade. General vasoconstriction was evident following WR1607 treatment in the dog as a decrease in pulse pressure was observed without a change in systolic pressure.[4]

In the present study WR1607 was given to monkeys prior to irradiation to investigate its effects on behavior and physiology during the period associated with radiation-induced early transient incapacitation.[13] It was anticipated that WR1607 would alleviate the behavioral and physiological decrement observed during this period.

## II. MATERIALS AND METHODS

Monkeys were used in this study to evaluate the ability of WR1607 to attenuate the early transient incapacitation induced by radiation. One group of 23 female monkeys (Macaca mulatta) was utilized to study the effects of WR1607 on aortic pressure, venous pressure, heart rate and respiratory rate both preirradiation and postirradiation. A second group of 24 male monkeys was utilized to evaluate the effects of WR1607 on the animals' ability to perform a learned task preirradiation and postirradiation. The two groups were subdivided as shown in Table 1.

Table I. Experimental Groupings

| Programmed dose (rads) | Average midline tissue dose ± S. E.* (rads) | WR1607 10 mg/kg | Number of animals |
|---|---|---|---|
| Physiology | | | |
| 0 | Control (sham irradiated) | yes | 5 |
| 2500 | 2230 ± 34 | yes | 6 |
| 4000 | 3680 ± 41 | yes | 6 |
| 15,000 | 14,830 ± 55 | yes | 6 |
| Behavior | | | |
| 2500 | 2450 ± 56 | yes | 6 |
| 2500 | 2630 ± 41 | no | 6 |
| 4000 | 4000 ± 26 | yes | 6 |
| 4000 | 4620 ± 10 | no | 6 |

* S. E. = Standard error of the mean

The animals in the group selected for physiological studies were placed in primate restraining chairs for 3 days before surgery. A 24-hour fast preceded all surgery. Atropine sulfate (0.05 mg/lb, I. M.) was given before surgery and anesthesia was induced with phencyclidine HCl (1 mg/kg, I. M.). A surgical plane was maintained with sodium thiopental. The surgical procedure consisted of placing catheters (PE160 polyvinyl tubing) into the femoral artery and vein and advancing the respective catheters into the aorta and vena cava. Paired frontal and occipital dural stainless steel screws were also placed on the calvarium to record the electroencephalogram (EEG). At this time only the cardiovascular data will be presented. The catheters were flushed daily with physiological saline containing 0.1 percent heparin. Postoperative antibiotic therapy (Bicillin,* 1 cc, I.M.) was initiated and continued for 5 days. The surgery was performed 5 days before irradiation. The aortic and

* Wyeth Laboratories, Philadelphia, Pennsylvania

venous pressure, heart rate and respiratory rate were monitored for 2 hours on the day before irradiation to establish a preirradiation base line.

The behavioral groups of animals were trained to perform a simultaneous task using shock motivation. The apparatus and training procedures have been previously described.[1] Trials were presented at 10-second intervals, with the animal given 5 seconds to respond to the correct key. If the animal failed to respond within 5 seconds or made an incorrect response, it received a brief electrical shock. Each test period consisted of 100 trials and lasted 16.7 minutes. The test periods started at 20-minute intervals giving the animal a brief rest period following each 100-trial session.

Food was withheld from the monkeys in all groups for 16 hours before irradiation; however, water was available ad libitum except for a period of approximately 3 hours. This 3-hour period without water included preparation of the animal for irradiation and the time spent in the exposure room. Approximately 90 minutes before irradiation the animals were transported to the exposure room and positioned at a distance from the radiation source calculated to give the desired dose. The behavioral animals were monitored while in an isolation cubicle within the exposure room. The appropriate connections were then made for monitoring either the physiology* or behavior.

The monkeys were positioned in the exposure room of the AFRRI-TRIGA reactor to receive the calculated dose. The average midline tissue dose (MTD) and the number of animals in each group are presented in Table I. The MTD was obtained

* Pressure transducers: arterial, Type P23Db; venous, Type P23BB, Statham Laboratories, Inc., Hato Rey, Puerto Rico
Eight-channel recorder, Model 7700, Hewlett-Packard Company, Rockville, Maryland

by determining the tissue kerma, free-in-air, at the midline exposure volume and multiplying this value by an experimentally derived factor (0.85). For these exposures the operation of the reactor and the characteristics of the radiation field were as previously described.[2]

Before injection of the WR1607 via the venous catheter (physiology) or saphenous vein (behavior) the animals were monitored for 20 minutes or a 100-trial session, respectively. A 10 mg/kg dose of WR1607 was injected 30 minutes before irradiation (prepared by dissolving the powder in 0.1 N NaOH and bringing the solution to volume with physiological saline, 5 mg/ml pH 10.5 to 11.0). The postinjection behavioral session was started 20 minutes before irradiation. The physiology animals were monitored for 1 hour postirradiation and the behavioral groups for 2 hours or six behavioral sessions postirradiation.

The behavioral data were tabulated at 10-trial intervals with a 90 percent correct response as the minimum acceptable criterion. The WR1607 injected animals' performance was compared to the noninjected animals' performance using the "exact" test.[8, 12] Latency values of the two groups were analyzed using the Wilcoxon signed ranks test.[12]

The physiological data were statistically analyzed using the analysis of variance with a one-way layout for equal or unequal group size.[11] Values were considered significantly different when $p < .05$.

## III. RESULTS

The aortic pressure, venous pressure, heart rate and respiratory rate of the groups of animals used in this study are shown in Figures 1–4.

Following the injection of WR1607 a significant ($p < .05$) increase occurred in the aortic pressure with a significant decrease in heart rate in all groups when compared to preinjection values. With the increase in aortic pressure a decrease in pulse pressure occurred due to a large increase in diastolic pressure. The venous pressure and respiratory rate also increased but not to a significant level over preinjection values. All indices, except for aortic pressure, tended to return toward preinjection levels after 15 minutes postinjection. The aortic pressure remained elevated for approximately 70 minutes postinjection.

After irradiation the respiratory rate increased significantly in all injected groups when compared to preinjection or control nonirradiated injected values. The aortic pressure decreased to significant levels in the 2500-rad group from 2-4 minutes postirradiation and in the 15,000-rad group from 1-2 minutes postirradiation when compared to preinjected values; but no significant change was observed in the 4000-rad group. When compared to the WR1607 injected controls, a significant difference in aortic pressure occurred from 1-30 minutes postirradiation in the 2500-rad group, from 1-5 minutes postirradiation in the 4000-rad group, and from 1-60 minutes postirradiation in the 15,000-rad group. The venous pressure and heart rate did not change significantly from preinjection values following irradiation. The heart rate in the 2500-rad group was significantly higher than the control injected group up to 10 minutes postirradiation.

The percent correct and latency data are presented in Figure 5 and Table II. Each point in Figure 5 represents either the percentage of correct responses or the average time required to complete a response during a 10-trial problem.

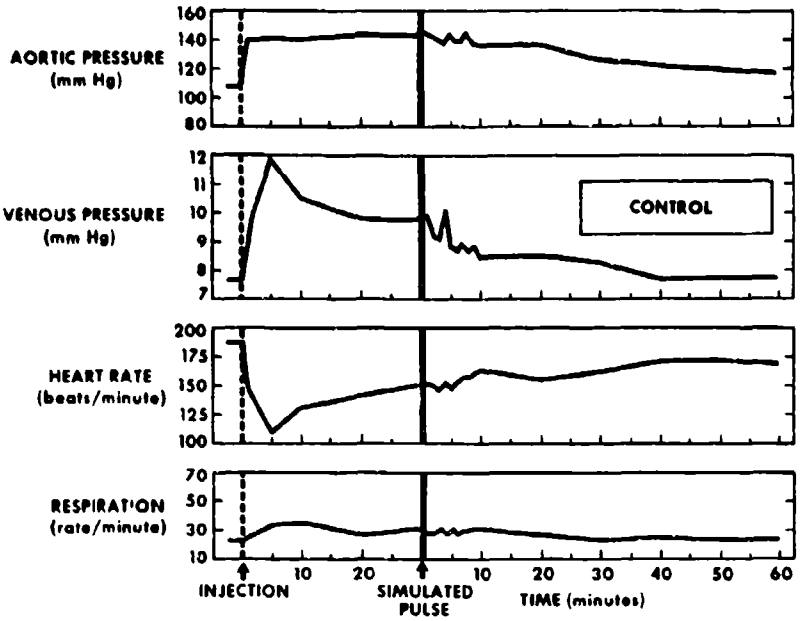


Figure 1. Physiology of control animals injected with 2-(n-decylamino) ethanethiosulfuric acid

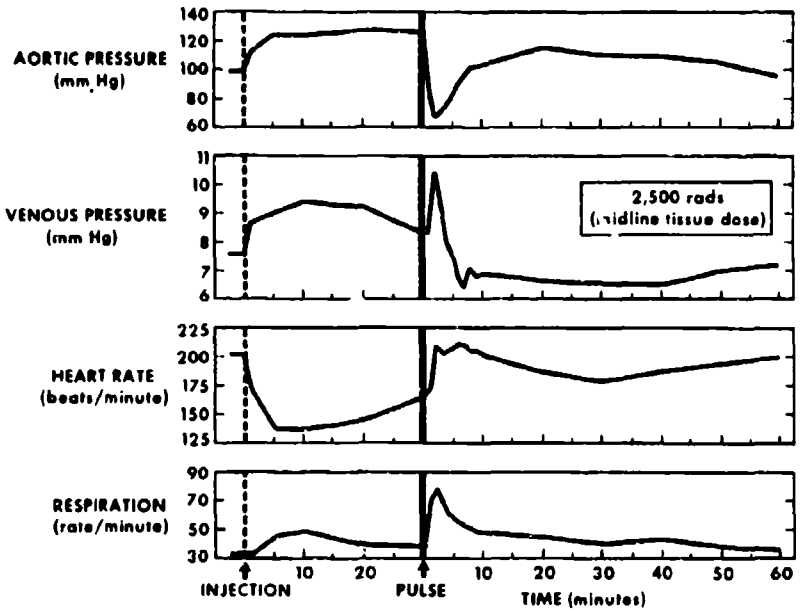


Figure 2. Physiology of animals injected with 2-(n-decylamino) ethanethiosulfuric acid and irradiated

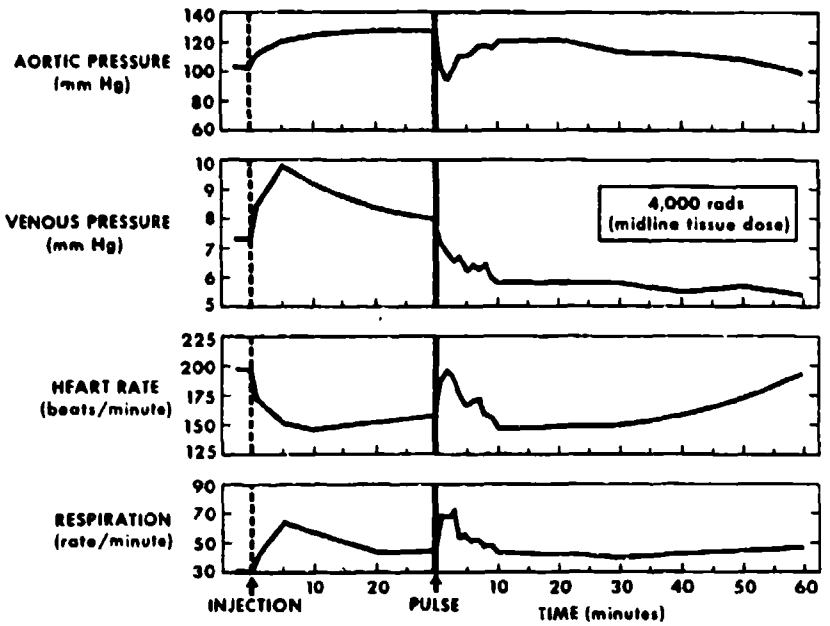


Figure 3. Physiology of animals injected with 2-(n-decylamino) ethanethiosulfuric acid and irradiated

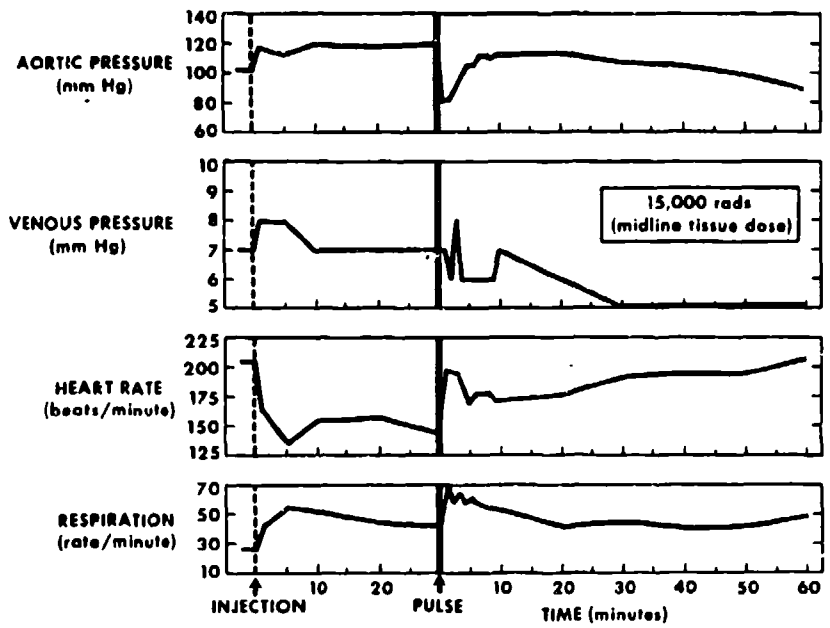


Figure 4. Physiology of animals injected with 2-(n-decylamino) ethanethiosulfuric acid and irradiated

No significant changes in percent correct trials or latency were observed in the session following the injection of WR1607. After irradiation a nonsignificant decrease in performance and a nonsignificant increase in latency occurred during the first four 10-trial blocks of problems of the first postirradiation session. Animals which did not receive WR1607 displayed changes to below acceptable values in these indices and did not return to preirradiation values during the first 100-trial session (Figure 5).

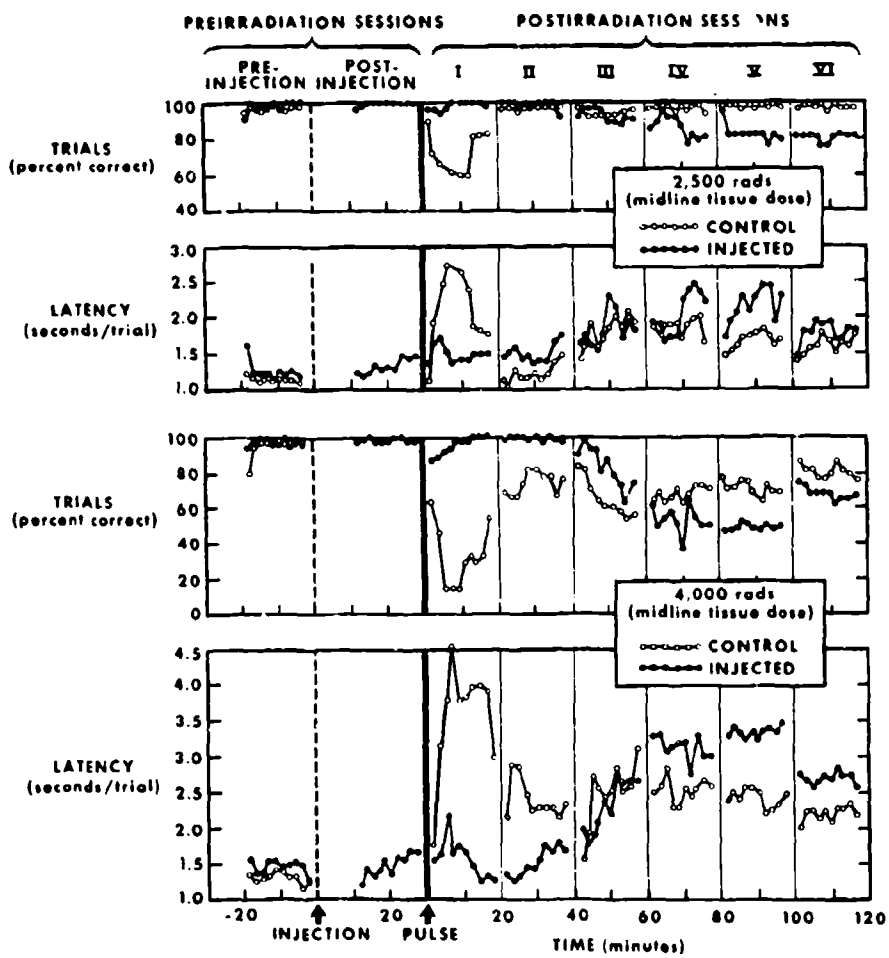


Figure 5. Behavioral response of animals injected with 2-(n-decylamino) ethanethiosulfuric acid and irradiated with 2500 or 4000 rads of mixed gamma-neutron radiation

Table II. Average Behavioral Response with Ranges before and following Irradiation

| Interval | Trials (percent correct) | | | | Latency (seconds/trial) | | | |
|---|---|---|---|---|---|---|---|---|
| | 2500-rad control | 2500-rad injected | 4000-rad control | 4000-rad injected | 2500-rad control | 2500-rad injected | 4000-rad control | 4000-rad injected |
| Preinjection | 99.2<br>98-100 | 97.8<br>94-100 | 96.8<br>95-100 | 98.0<br>95-100 | 1.13<br>.98-1.98 | 1.25<br>.95-1.69 | 1.32<br>.83-1.87 | 1.49<br>.88-1.89 |
| Postinjection | -- | 99.5<br>99-100 | -- | 98.3<br>98-100 | -- | 1.31<br>1.02-1.79 | -- | 1.61<br>.94-1.96 |
| Pulse | | | | | | | | |
| 0-10 minutes | 71.3<br>34-98 | 99.5<br>92-100 | 29.6*†<br>10-64 | 91.5<br>76-100 | 2.16*<br>1.11-2.64 | 1.79<br>.98-2.63 | 3.42*†<br>1.06-5.00 | 1.79<br>1.10-3.11 |
| 10-20 minutes | 73.4<br>0-100 | 99.7<br>98-100 | 36.6*†<br>0-96 | 98.8<br>96-100 | 2.09*<br>1.76-2.64 | 1.43<br>.92-2.01 | 3.75*†<br>1.10-5.00 | 1.43<br>.80-1.76 |
| 20-40 minutes | 99.0<br>98-100 | 99.0<br>97-100 | 72.3*<br>3-94 | 98.9<br>98-99 | 1.21*<br>.97-1.40 | 1.49<br>.94-1.81 | 2.18*<br>.78-4.71 | 1.56<br>.98-2.05 |
| 40-60 minutes | 94.5<br>83-100 | 93.2<br>84-98 | 63.8*<br>20-97 | 82.0<br>59-96 | 1.79*<br>1.05-2.34 | 1.81*<br>1.18-2.24 | 2.49†<br>1.19-4.10 | 2.31*†<br>1.49-3.21 |
| 60-80 minutes | 97.7<br>95-99 | 87.2<br>41-100 | 67.0*<br>0-98 | 54.2*<br>0-97 | 1.84*<br>1.29-2.48 | 2.06*<br>1.27-2.71 | 2.53†<br>1.48-5.00 | 3.15*†<br>1.48-5.00 |
| 80-100 minutes | 98.8<br>96-100 | 83.3<br>10-100 | 70.6<br>1-98 | 48.8*<br>0-98 | 1.67*<br>.99-2.21 | 2.14*<br>1.01-4.48 | 2.34*<br>.86-4.32 | 3.36*†<br>1.43-5.00 |
| 100-120 minutes | 98.7<br>96-100 | 81.3<br>0-100 | 79.2<br>38-99 | 69.0<br>5-99 | 1.60*<br>1.08-2.21 | 1.98*†<br>1.14-5.00 | 2.23*†<br>.89-4.20 | 2.70*†<br>.99-5.00 |

* Significantly different from WR1607 treated group at .05 percent level
† Significantly different from own preinjection group at .05 percent level

The animals receiving WR1607 maintained percent correct and latency values near preirradiation levels until the third session postirradiation (40-60 minutes). During the fourth session following irradiation (60-80 minutes), in both the 2500- and 4000-rad WR1607 treated groups, the percent correct responses decreased. The WR1607 injected animals' values were not significantly different from the control groups' values for any behavioral session after the first 100-trial session post-irradiation (0-20 minutes).

Following the injection of WR1607 the animal appeared to become very apprehensive with increased movement in the restraining chair. In most instances the animal vocalized during the injection. This period of increased activity lasted for 7-10 minutes postinjection and usually culminated in the animal vomiting 8-10 minutes postinjection. After the animal vomited the period of apprehension appeared to end with no further overt effects of the drug being evident.

Following irradiation the WR1607 treated animals appeared much more alert than nontreated animals for 30 to 40 minutes. After 40 minutes postirradiation there was no discernible difference.

## IV. DISCUSSION

The data obtained in this study show WR1607 to be beneficial in eliminating the early transient incapacitation (ETI) period observed in monkeys receiving a single pulse of 2500 or 4000 rads of radiation.

The physiological mechanisms which produce the ETI period in the monkey after a supralethal dose of radiation are unknown. Therefore, it is not possible to define the mechanisms by which WR1607 is able to attenuate the radiation effect in the monkey. From the data presented in this study it would appear that a state of hypertension was induced by WR1607 through the beta adrenergic-like properties attributed to the compound.[4] Other investigations have indicated that the ETI may be initiated by a change in blood flow to various areas of the brain.*,[14,16] Pretreatment with WR1607 because of its adrenergic properties may inhibit these changes, thus alleviating the ETI period.

*Unpublished: Turbyfill, C. L. and Flinton, J. H., Armed Forces Radiobiology Research Institute, Bethesda, Maryland

The chemical properties of WR1607 must also be considered to elucidate the mechanisms by which this class of compounds attenuate radiation injury. Since the aminoethanethiols can be cleaved hydrolytically, the radioprotective mechanism of WR1607 may be due to a release of sulfides by hydrolysis, freeing the thiol group to form mixed disulfides.[6,7] However, the radioprotective mechanisms of WR1607 are at this time speculative and further research in this area is needed.

Although WR1607 shows promise as a radioprotective compound, it has properties which may limit its use in man.[4] It must be given prior to irradiation in order to obtain the radioprotective effect. In addition, side effects such as cardiac toxicity and vasoconstriction occur following its administration. In the present study a dose of 10 mg/kg was used which is approximately one-third the $LD_{50}$ dose. At this level the undesirable effects were observed but the degree of physiological or behavioral impairment did not exceed acceptable limits. However, due to the toxic properties of WR1607, future investigative effort will be conducted with less toxic compounds, such as S-2-(3-aminopropyl) aminoethyl phosphorothioic acid (WR2721AF).

## V. SUMMARY

2-(n-decylamino) ethanethiosulfuric acid (WR1607) was given to monkeys (10 mg/kg) 30 minutes prior to irradiation to investigate its effects on behavior and physiology during the early incapacitation period. Following the injection of WR1607 a significant increase occurred in aortic pressure with a significant decrease in heart rate. No significant changes in percent correct trials or latency occurred following the injection of WR1607 in trained monkeys. After irradiation with 2500, 4000, or 15,000 rads the WR1607 injected animals displayed a decrease in aortic pressure from the

elevated levels following injection. The decrease in aortic pressure was significantly different from preirradiation values 2-4 minutes postirradiation in the 2500-rad group and from 1-2 minutes in the 15,000-rad group. The respiratory rate increased significantly in all irradiated groups postirradiation. Trained monkeys receiving WR1607 did not display a decrease in performance during the usual FTI period (0-20 minutes postirradiation) following a dose of 2500 or 4000 rads. Trained monkeys not receiving the drug all displayed a decrease in performance below a 90 percent correct response level in both the 2500- and 4000-rad groups. The physiology and behavior of WR1607 treated and untreated animals were not significantly different after the first 20-minute postirradiation period.

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